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Investigation of changes in the enzymatic function of the liver of rabbits, caused by established exogenous and endogenous toxicosis

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Abstract
Objective: Identify changes in the enzymatic function of the liver by creating a model of exogenous and endogenous intoxication in the experiment.
Materials and methods: The experiments were conducted on 48 rabbits of the genus "Chinchilla". Rabbits were divided into three groups: rabbits, included in group I, were subjected to intoxication by inhalation of HCl vapor. In rabbits included in the 2nd group, a model of intestinal obstruction was created. Speaking about the experimental animals included in group III, it should be noted that they also created a model of exotoxicosis and the solution of riditox was introduced into the abdominal cavity. Rabbits for the control group were intact, and the results obtained from them were considered normal. The activity of the enzymes aspartate aminotransferase (AsAT), alanine aminotransferase (AlAT) and lactate dehydrogenase (LDH) was determined in the blood of rabbits using a "Bioscreen MS 2000" microanalyzer.
Results: The results showed that intoxication caused by inhalation of HCl impairs the antitoxic function of the liver, and the resulting toxic substances have a negative effect on the synthesis of liver enzymes. This is manifested in the dynamics of the activity of the enzymes AsAT, AlAT and LDH in the blood. Thus, the activity of the AsAT enzyme in the blood during HCl intoxication was on average increased by 2.1-2.5 times or 110.4-149.4%, AlAT activity increased 1.6-2.5 times or 104.2% - 148.1%. However, the activity of the LDH enzyme in the experiment increased by only 8.8-27.8%. Similar results were observed in the dynamics of intestinal obstruction.
Conclusion: It was concluded that intoxication of both exogenous and endogenous origin causes a significant impairment of enzyme synthesis in the liver. Thus, activation of all three enzymes (AsAt, Alat, LDH) in the blood was observed when inhaling HCl vapors (exotoxicosis), as well as in case of intestinal obstruction (endotoxicosis). However, the activity of the LDH enzyme increased insignificantly compared to AsAT and AlAT.

Keywords: exogenous and endogenous intoxication, intestinalobstruction, liver

Introduction
The development of industry, unsatisfactory environmental conditions, the spread of alcoholism and drug addiction exposes the body to constant exposure to harmful substances. As a result, a variety of intoxications develop in the body. For this reason, exotoxicosis and endotoxicosis has become an object of study for many scientists (Puchalsky AL. *et al*, 2004; Luzhnikov EA. *et al*, 2008; Vertkin AL. *et al*, 2009;. Garbuzenko DV. *Et al* 2014) [13, 12, 14, 5]. The development of endogenous intoxication, impaired physiological functions of the body, leads to the destruction of vital organs. One of the target organs of exogenous and endogenous intoxication, as well as, possibly, the first among them, is the liver (Goryachev A.N. *et al*., 2008; Garayev G.S. *et al*., 2010; Chistyakova M.V. and *et al*., 2012) [6, 4, 3]. The normal physiological function of the liver during intoxication, which develops inside the body and, as a result of external factors, is impaired. The resulting dysfunction affects the tissues and causes differential changes in cell metabolism, disrupting the balance of physiological processes in them. The toxic effect of these intermediates causes the formation of irreversible processes in cells, tissues, organs and the whole body (Abe *et al*., 2007) [1]. Factors affecting liver failure during endotoxicosis and exotoxicosis have not yet been described in detail. Thus, with the pathology of the lymphatic circulation of the liver and the microcirculatory network, changes in the enzymatic function of this organ are not clear.

The aim of th ework
The aim of the study was to find out changes in the enzymatic function of the liver by creating a model of exogenous and endogenous intoxication in rabbits in the experiment.

Materials and Methods
The study was conducted at the Department of Human Anatomy of the Azerbaijan Medical University and at the Research Center of this university.
The experiments were carried out on 48 rabbits of the Chinchilla genus. Rabbits are divided into groups in accordance with the proposed experiments. Rabbits, included in group 1, were subjected to intoxication by breathing acid HCl through a special chamber. In rabbits included in group 2, a model of intestinal obstruction was developed. In the experimental animals included in group 3, as well as in group 1, a model of exotoxicosis was created and the Ridutox solution was entered into the abdominal cavity of these animals. Rabbits included in group 1 are divided into 3 subgroups depending on the purpose of the experiment. We studied the activity of liver enzymes in animals on the 10th day of the experiment (1st subgroup), the 30th day (2nd

subgroup) and the 60th day (3rd subgroup).

During the formation of a model of intestinal obstruction, 1 ml of callipsol solution was injected into the abdominal cavity of the experimental animals, and the abdominal cavity was opened after anesthesia was achieved by a midline incision. After reaching the cecum on the border between the cecum and the small intestine, a turunda was performed and the intestine was tied up. Then the abdominal cavity was sewn in layers in a hermetic way. On intact rabbits, taken for the control group, studies were conducted, and the results were taken as the norm. Results were compared with results obtained from other animals.

Animals used in the experiment were treated in accordance with the rules of the European Commission on Bioethics.

The activity of aspartate aminotransferase (AsAT), alanine aminotransferase (AlA) and lactate dehydrogenase (LDH) enzymes was determined in the blood of rabbits. The definition of these enzymes is based on the rules described in the corresponding literary guides [Kushkin AA, 2010; Karpischenko A.I. *et al*, 2014] [10, 8], using reagent kits made in the Czech Republic by means of the Bioscreen MS-2000 microanalyzer operating in full automatic mode.

Digital research data were statistically processed in accordance with the general rules for medical and biological research. To estimate the difference between variational series, the parametric Student's t test was used; then, the nonparametric Wilcoxon U-test (Mann-Whitney) was used to identify and compare the significance of the difference in groups and subgroups. The minimum (min) and maximum (max) values, the average value (M ± m), the difference between the groups (P) were calculated. In the calculations, the application programs "Statistical" (Statsoft, 1999) and Microsoft Excel Windows-7 [Borovikov VP., 2015] [2] were used.

Results & Discussion

The results of our experiments show that the development of intoxication by inhalation of HCl vapors violates the antitoxic function of the liver, and the resulting toxic agents have a negative impact on the function of the synthesis of liver enzymes. The experimental results show that the average activity of the AsAT enzyme in the intact group is 0.099 ± 0.007 mmol /l, the minimum limit is 0.04 mmol l, and the maximum limit is 0.14 mmol /l. The activity of the AsAT enzyme in the blood increased 1.6 times (P <0.001) or 64.5% compared with the intact group on the 10th day of the experiment in animals belonging to the 2nd subgroup. The average concentration of this enzyme ranges from 0.12 to 0.21 mmol / l to 0.158 ± 0.008 mmol / l. The minimum activity of the AsAT enzyme activity in the bloodstream increased by 3 times (P <0.001), and the maximum limit was 0.07 mmol / l (P <0.001) as compared with the intracellular state on the 10th day of the experiment (Table 1).

Talbe 1: Changes in the concentration of enzymes in the blood of rabbits inhaling HCl vapors

Investigated parameters	Statistical data	Groups			
		Intact animals (n=16)	After inhalation of HCl		
			10 (n=12)	30 (n=8)	60 (n=4)
AsAT, mmol/l	M±m	0,096±0,007	0,158±0,008	0,203±0,012	0,24±0,019
	Min	0,04	0,12	0,16	0,20
	Max	0,14	0,21	0,25	0,29
	P	-	<0,001	<0,001	<0,001
AlAT, mmol/l	M±m	0,099±0,07	0,163±0,008	0,208±0,011	0,245±0,019
	Min	0,05	0,12	0,16	0,21
	Max	0,14	0,21	0,25	0,29
	P	-	<0,001	<0,001	<0,001
LDH, mmol/l	M±m	297,4±11,9	319±14,3	323,6±20,1	380±33,9
	Min	225	240	260	300
	Max	375	390	410	450
	P	-	>0,05	>0,05	>0,05

Note: 1. n – number of observations; 2. Minimum and maximum values of parameters; 3. M±m – average mathematical value; 4. P –comparison between groups.

In animals of the 3rd subgroup inhaling HCl vapors, on the 30th day of the experiment, the activity of the AsAT enzyme increased and the average quantitative value of this parameter was 0.203 ± 0.012 mmol / l. The minimum degree was 0.16 mmol / l, the maximum degree was 0.25 mmol / l. This level indicates that the enzyme activity in the blood is higher by 2.1 times or 110.4% compared with the intact group (P <0.001).

In animals of the 4th subgroup, which also inhaled HCl vapors, on the 60th day of the experiment, the mean digital value of the AsAT enzyme was 0.240 ± 0.019 mmol / l. At the same time, the minimum level of the parameter was 0.2 mmol / l, the maximum - 0.29 mmol / l. Thus, on the 60th day of the experiment, the average activity of the AsAT enzyme increased by 149.4% or 2.5 times compared with the intact group (P <0.001). The minimum level increased 5 times in comparison with the intact group (P <0.001), the maximum level increased 2 times (P <0.001).

The analysis of digital parameters obtained during the creation of intoxication by inhalation of HCl vapors showed that, as compared with the 10th day, on the 30th day, the activity in the blood of the AsAT enzyme increased by 27.9%, (P <0.001), on the 60th day - by 51.6%. Thus, inhalation of HCl vapors dramatically impairs the function of enzyme synthesis by the liver. It shows itself on the dynamics of changes in the AsAT enzyme in the blood.

Studies have shown that inhalation of HCl vapor also affects the activity of the enzyme AlAT. In the intact group, the average concentration of the AlAT enzyme is 0.099 ± 0.007 mmol / l. The minimum level is 0.05 mmol / l, the maximum level is 0.14 mmol / l. In the 2nd group, the activity of the AlAT enzyme, as compared with the intact group, was increased 1.6 times (P <0.001) or 104.2% by the 10th day of the experiment. The enzyme activity varied in the interval 0.12-0.21 mmol / l, on average was equal to 0.163 ± 0.008 mmol /l.

In experimental animals included in the 3rd subgroup on the 30th day of the experiment, the activity of the AlAT enzyme increased even more, and the average digital value reached 0.2008 ± 0.011 mmol / l. The minimum level at the same time was 0.16 mmol/l, the maximum was equal to 0.25 mmol/l. The observed level compared with the intact group is higher at 2.1 (P <0.001) or 110.1%. Also the minimum and maximum concentration levels of the AlAT enzyme increased dramatically. The minimum level was even more than 3 times.

In animals of the 4th subgroup, on the 60th day of the experiment, the activity of the AlAT enzyme increased 2.5 times (P <0.001) or 148.1% compared to the norm. Thus, the average digital value of its activity was 0.245 ± 0.019 mmol / l. The minimum level was 0.21 mmol / l, the maximum level reached 0.3 mmol / l. As can be seen, the minimum and maximum activity levels in the blood of the AlAT enzyme differ sharply from the intact group.

Analysis of the data obtained from the dynamics of development during intoxication with HCl vapors shows that on the 30th day in the blood the activity of the enzyme AlAT increases by 27.7% compared to the 10th day, and by 50.8% on the 60th day. It should be noted that the activity of the enzyme AlAT, as well as the activity of the enzyme AsAT, is increased dramatically. Thus, during intoxication caused by inhalation of HCl vapors, the enzymatic function of the liver significantly changes and the activity of the AlAT enzyme increases, on the 60th day of the experiment it becomes 2.5 times more normal (P <0.001).

The results of the experiments show that after inhaling HCl vapors, the average digital value of the activity of the LDH enzyme in the blood is 319 ± 14.3 u / l. The minimum level is 240 u / l, the maximum - 390 u / l. In the intact group, the average activity of this enzyme was 297.4 ± 11.9 u / l, the minimum level was equal to 225 u / l, the maximum level was 375 u / l. Thus, on the 10th day of the experiment, compared with the intact group, the activity of the LDH enzyme increased by only 7.3%. Both levels of this enzyme compared with the intact group changed slightly.

We observed similar patterns on the 30th day of the experiment on animals belonging to the 3rd subgroup. Thus, the mean activity of the LDH enzyme in the blood was 323.6 ± 20.14 u / l, the minimum level was 260 u / l, the maximum was 410 u / l, and increased by 8.8% compared to the intact group. Again the difference in level changes is insignificant. On the 60th day of inhalation of HCl vapor (4th subgroup), the LDH activity in the blood increased slightly compared with the intact group, and this difference was 27.8% (P <0.05).

Therefore, the average activity in the blood of the studied enzyme was 380 ± 33.9 u / l, the minimum level was equal to 300 u / l, the maximum 450 u / l. As you can see, both levels are 75 units more than normal. Analysis by subgroups of the dynamics of LDH enzyme changes during intoxication created by inhalation of HCl vapors shows that compared to the 10th day, on the 30th day, the enzyme activity practically did not change (increased by only 1.4%). On the 60th day, this difference, slightly increased, amounted to 19.1%.

Thus, during intoxication created by inhalation of HCl vapor, the activity of the LDH enzyme, although it increases, but in comparison with other studied enzymes, does not change dramatically.

Based on the results of these experiments, it can be said that exotoxicosis increases the enzymatic function of the liver. As the period of intoxication increases, the enzymatic activity of the hepatocytes of the liver becomes more and more disturbed.

As the inhalation time of a toxic substance increases, the changes that occur in the function of enzyme synthesis deepen. On the other hand, an analysis of the data obtained shows that with intoxication caused by inhalation of HCl vapor, the changes resemble hepatitis. The reason is that the plasma activity of the enzymes AsAT and AlAT increase dramatically.

This idea is also confirmed by the fact that the blood concentration of medium molecular peptides increases.(Laberko LA. *Et al*, 2000; Kamyshnikov BS., 2003; Kerimov RD., 2014)[11, 7, 9].

One of the tasks assigned to the study was to determine whether changes in liver function depend on the genesis of endogenous intoxication. To solve this problem, a model of intestinal obstruction was created on experimental animals. As is known, in case of intestinal obstruction, the causes of endogenous intoxication are, on the one hand, toxic substances formed during destructive processes in tissues, on the other hand, substances that are associated with the vital activity of pathogenic microflora in the intestine (Table 2).

Table 2: Changes in the concentration of enzymes in the blood of rabbits with an established intestinal obstruction model.

Para-meters	Statistical data	Groups			
		Intact animals (n=16)	After inhalation of HCl (days)		
			10 (n=12)	30 (n=8)	60 (n=4)
AsAT, mmol/l	M±m	0,096±0,007	0,199±0,012	0,239±0,014	0,239±0,014
	Min	0,04	0,12	0,18	0,18
	Max	0,14	0,25	0,3	0,3
	P	-	<0,001	<0,001	<0,001
ALAT, mmol/l	M±m	0,099±0,07	0,195±0,010	0,229±0,022	0,295±0,032
	Min	0,05	0,14	0,15	0,21
	Max	0,14	0,25	0,3	0,35
	P	-	<0,001	<0,001	<0,001
LDH, mmol/l	M±m	297,4±11,9	372,3±11,3	400,1±14,9	412,5±20,2
	Min	225	300	340	370
	Max	375	420	450	460
	P	-	<0,001	<0,001	<0,001

Note: 1. n – number of observations; 2. Minimum and maximum values of parameters; 3. M±m – average mathematical value; 4. P –comparison between groups.

On the 3rd day of creating a model of intestinal obstruction in blood plasma, the increase in AsAT activity continued. The minimum level increased 4.5 times, the maximum - more than 2 times (P <0.001). Compared with the intact group, in the blood plasma after the 3rd day of the intestinal obstruction model, the activity of the AsAT enzyme increased 2.5 times (P <0.001) or 14.8%. Analysis of the dynamics of intestinal obstruction shows that the activity of the AsAT enzyme on the 3rd day of the experiment was 19.9% more than the 1st day (P <0.01), compared to the 2nd day 38.1 % or 1.4 times (P <0.01).

The increase in activity in the blood plasma of the AsAT enzyme while creating a model of intestinal obstruction continued 5 days after the start of the experiment. Digital data compared with the intact group were more than 2.9 times or 185.7%. Thus, the mean digital plasma value of AsAT activity was 0.275 ± 0.022 mmol / l. The minimum level was 0.22 mmol / l, the maximum reached 0.32 mmol / l. Thus, with the development of intestinal obstruction, the enzymatic function of the liver is impaired.

Similar changes can be observed when determining the activity of the enzyme AlAT. So, after the 1st day of creating a model of intestinal obstruction, the activity of AlAT enzyme in the blood increased by 2.0 times (P <0.001) or by 97.5% compared with the intact group.

On the 3rd day of creating a model of intestinal obstruction in plasma, the activity of the AlAT enzyme increases even more and reaches a digital value of 0.229 ± 0.022 mmol / l. The minimum level is 0.15 mmol / l, the maximum is 0.3 mmol / l. Although the minimum and maximum digital values differ insignificantly compared to the values of the 1st day, the average digital value is 2.3 times higher (P <0.001) or 131.5% compared to the intact group.

After the 5th day of the experiment, the activity of the AlAT enzyme increased 3 times (P <0.001) compared with intact group, and the average value of its activity was 0.2295 ± 0.032 mmol / l, the minimum limit was 0.21 mmol / l, and the maximum the limit was 0.35 mmol / l.

The dynamics of changes in the LDH enzyme in the blood plasma was not expressed in the dynamics of the development of the intestinal obstruction model. On the 3rd day its growth was only 7.5%, and on the 5th day - 10.8%.

Analysis of the results of experiments shows that intestinal obstruction in rabbits led to a sharp increase in the activity of all three enzymes, in particular the enzymes AsAT and AlAT. However, the activity of the LDH enzyme is reduced relative to the activity of the enzymes AsAT and AlAT.

Conclusion

Experimental results prove that intoxication, both exogenously and endogenously, is the main violation of the synthesis of enzymes in the liver. Thus, activation of all three enzymes (AsAt, AlAT, LDH) in the blood was observed during intoxication (exotoxicosis), and also in case of intestinal obstruction (endotoxicosis) during inhalation of HCl vapor. However, the activity of the LDH enzyme is slightly increased compared with other enzymes.

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